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Molecular dynamics of the pyridoxine derivative in the acetylcholinesterase active cavity

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Abstract

Acetylcholinesterase (AChE) is a key enzyme in central nervous system, responsible for the regulation of nerve impulse transmission through the rapid hydrolysis of the acetylcholine neurotransmitter. In recent years, the issue of AChE specific interaction with ligands to regulate its activity becomes more and more popular. In particular, it is necessary to develop specific AChE inhibitors - potential new drugs for the treatment of neurodegenerative diseases, which will have a greater efficacy and fewer side effects. Currently, the methods of molecular modeling are actively used for the development of new drugs. In this paper we studied the insilico structure of a mouse AChE, since the study of enzyme activity in preclinical tests was carried out on mice. Pyridoxine derivative was used as ligands for which anticholinesterase symptoms were shown during the initial experiments invivo, and its position in the active center during the docking was similar acetylcholinesterase inhibitors used in medicine nowadays (proserin, physostigmine). The use of molecular dynamic simulation method allowed to evaluate the drug potential of inhibitors by the most cost -effective way. The study was conducted using the software package NAMD 2.8 and the force field AMBER 99. The study showed that the spatial position of ligand is favorable for AChE inhibiting. As the result of the molecular dynamics, the distance between the oxygen of the hydroxyl group Ser203 and the carbon atom of derived pyridoxine fragment carbamylation decreased from 6.4 Å to 3.8 Å, which contributes to their interaction to form a bond. The spatial position of the ligand is supported by the weak link between the tertiary nitrogen of carbamylation fragment and the oxygen of hydroxyl group Tyr124 AChE. Moreover, the ligand is held in an active cavity of the enzyme by hydrophobic interaction of its heterogenic cycle with Trp86 AChE. This state of the ligand structure may provide a long-term anticholinesterase of pyridoxine effect producers.

Keywords

Acetylcholinesterase (AChE), Molecular dynamics, Pyridoxine derivative, Specific interaction of enzyme with ligand